Wearing Off, Dyskinesia, and the Use of Continuous Drug Delivery in Parkinson's Disease

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KEYWORDS

• Parkinson's disease • Dyskinesia • Wearing off • Drug delivery • Rotigotine

KEY POINTS

- The long-term treatment of Parkinson's disease (PD) requires consideration regarding the nature of dopaminergic treatment used to control motor symptoms, both in the early and late stages of the illness.
- The concept of continuous dopaminergic stimulation has altered the face of treatment by persuading clinicians that early use of a dopamine agonist can protect against the onset of wearing off and dyskinesia.
- A mantra for treating PD is to adopt a philosophy of applying drug treatment as continuously as possible, irrespective of whether the therapy is L-dopa or a dopamine agonist.
- Rotigotine delivered by a transdermal patch exemplifies continuous drug delivery, and its ability to control wearing off and potentially avoid dyskinesia in patients with PD.
- Rotigotine supports the concept of delivering pharmacologic agents continuously in a clear and concise manner that is relevant to not only clinical trials but also to the everyday treatment of PD and to routine clinical practice.

INTRODUCTION

The pharmacologic treatment of Parkinson's disease (PD) is dominated by the use of L-dopa (also known as levodopa) and dopamine agonists to control motor symptoms.[1] Older ergot-related dopamine agonists such as bromocriptine and pergolide are no longer in common use owing to safety concerns over pulmonary fibrosis and cardiac valvulopathy,[2] which do not occur with the nonergot derivatives ropinirole, pramipexole, and rotigotine. The long-term use of dopamine replacement therapy demonstrated that with disease progression, motor fluctuations, characterized by "wearing off" and

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motor complications in the form of dyskinesia, become increasingly problematic in maintaining symptomatic control.[3] Both symptoms are more associated with the use of L-dopa than with dopamine agonists; the basis of this concept is discussed in this review. Although dyskinesia is considered a more significant event, wearing off affects quality of life to a greater extent.[4] These complications of therapy dictate the manner whereby patients with PD are treated from diagnosis until the late stages of the illness.

The onset of either wearing off or dyskinesia commonly signals the risk of the appearance of the other, but each does not necessarily occur in the same individual, and differences in causative factors are not understood.[5,6] Both occur more frequently with the worsening of motor symptoms and with the extent and duration of drug treatment,[3] which suggests that there is an opportunity to modify their onset and progression. However, the pathophysiology of wearing off or dyskinesia is not fully understood, and the most appropriate way of applying dopaminergic therapy remains debated. This review looks at the current concepts underlying the genesis of both wearing off and dyskinesia in PD, and suggests that using an approach to treatment based on continuous drug delivery (CDD) may be a step forward in the control of these symptoms.[7]

WEARING OFF

Wearing off is defined as a gradual decrease in the duration of effect of each dose of medication. It will eventually affect all patients with PD, but it is currently underrecognized and is not considered an early event in the course of treatment.[8] Nevertheless, wearing off can appear within months or a few years of starting therapy, depending on dose, as observed in a significant proportion of patients in studies of the early use of L-dopa in PD (Earlier vs Later Levodopa Therapy in Parkinson's Disease [ELLDOPA] and Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease [STRIDE-PD]).[9,10] Sometimes neither physicians nor patients are aware that adjustments to treatment regimens in early PD indicate the onset of wearing off and that the signs are not limited to the return of motor symptoms, but can first become apparent in relation to nonmotor symptomatology.[8] Wearing off in patients with PD is treated by alterations in the dosage or timing of L-dopa administration or by the addition of a longer-acting dopamine agonist; however, the manner whereby this is undertaken may affect the outcome, as discussed later.

Because the pharmacokinetic profile of L-dopa does not change over the course of PD or with the onset of wearing off, some centrally mediated pharmacodynamic changes in L-dopa's actions seem to be crucial.[11] The concept of the cause of wearing off is linked to the continuing degeneration of nigrostriatal dopaminergic neurons in the progression of PD. This process is deemed to lead to reduced presynaptic handling and storage of dopamine derived from L-dopa, and to a reduced buffering of striatal dopamine receptors from the fluctuations in plasma concentrations of L-dopa that occur over the course of the day.[8] Certainly the duration of effect of a single dose of L-dopa in patients with early PD exceeds that expected from the 90-minute plasma half-life of the drug, which supports the storage concept. However, this explanation may be simplistic, as wearing off can occur in response to dopamine-agonist treatment whereby only postsynaptic responses are involved,[12,13] although to a lesser degree than with L-dopa. Similarly, in experimental models of PD where the majority of dopaminergic neurons have been destroyed by the use of 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), wearing off occurred with repeated pharmacologic treatment.[14] The nature of these postulated postsynaptic changes is not known, and it is generally presumed that they involve striatal

output from D-2 receptors that are considered the source of symptomatic improvement in motor symptoms in patients with PD. An alternative explanation lies in the differences in pharmacology of L-dopa and dopamine agonists, with the former also inducing D-1 receptor stimulation that may contribute to the improvement in motor symptoms, which may explain the accepted greater efficacy of L-dopa compared with D-2 selective dopamine agonists. This point may be important, because it is clear that repeated stimulation of D-1 receptors leads to a rapid desensitization and tolerance to drug effects, perhaps induced by an internalization of receptors.[15] The result would be a decreased duration of drug response to L-dopa as occurs in wearing off in PD patients, but this would not sufficiently explain why adding a dopamine agonist "cures" wearing off.

One other component of the actions of dopaminergic drug action may also contribute to the onset of wearing off: the complex issue of the short-duration and long-duration response (SDR and LDR).[16,17] The terms SDR and LDR are generally used to describe the effects of L-dopa but can also apply to dopamine agonists. SDR is the immediate effect of treatment seen after each dose of the drug, and fades within a few hours. LDR is the effect of a drug that takes 2 to 3 weeks to become established after treatment is initiated and then disappears slowly after stopping treatment, with a return to a higher level of disability similar to that seen between doses during treatment. Wearing off might immediately be thought to represent a shortening of SDR but, perhaps surprisingly, it has been shown to involve a loss of LDR. However, because the pathophysiologic basis of LDR is not understood,[18] it is perhaps not helpful when considering the practical issues of controlling wearing off.

DYSKINESIA

Dyskinesia is, in general, described as a single entity but actually comprises chorea, dystonia, and athetosis that can be focal, segmental, or generalized.[19] This distinction serves to emphasize the complexity of the underlying pathophysiology that remains poorly understood. Dyskinesia appears to be a postsynaptic phenomenon because it does not usually occur in humans or animals with an intact nigrostriatal pathway. Pharmacologic doses of L-dopa failed to produce dyskinesia in healthy animals when administered on a chronic basis or in humans without PD who were treated with L-dopa for many years.[20,21] One exception is that large toxicologic doses of L-dopa did induce dyskinesia in healthy primates,[22] which suggests a role for drug treatment (see later discussion).

By contrast, the administration of L-dopa to 6-OHDA–lesioned rats or in MPTP-treated primates with greater than 90% loss of striatal dopaminergic input produced involuntary movements very quickly, sometimes even after a single dose.[23,24] Similarly, in human studies the administration of L-dopa in MPTP-treated drug addicts, individuals with previously untreated late stage PD, or those with young-onset PD rapidly induced dyskinesia (and incidentally, wearing off), reflecting the underlying severity of nigral dopaminergic cell loss.[25–27] Indeed, there is little doubt that the primary predisposing factor for dyskinesia induction is the extent of nigral cell degeneration, which dictates the dose and duration of treatment with L-dopa required to induce dyskinesia. A recent reanalysis of the STRIDE-PD study showed age, disease severity, L-dopa dose, gender (female), body weight, and United States location as significant factors in determining the prevalence of dyskinesia.

The appearance of dyskinesia in patients with PD has 2 major components: (1) a priming process that lays down a motor memory for the expression of abnormal involuntary movements (AIMs), and (2) the expression of dyskinesia that then occurs in

response to each dose of dopaminergic medication.[28,29] Priming is the least well-understood component, but its persistent, if not permanent, nature suggests fundamental change in basal ganglia output; this may involve complex changes in intracellular signaling and alterations in processes such as long-term potentiation and long-term depression. Substantial evidence in the literature links dyskinesia to D-1 receptor function, and is considered to be the reason why dyskinesia appears more commonly with L-dopa than with D-2 selective dopamine agonists (see, eg, Berthet and colleagues[30]). In turn, this implicates the direct striatal output pathway and the involvement of the internal segment of the globus pallidus, as shown in classic models of basal ganglia function. However, because these data come from experimental models of PD (the AIMs model in 6-OHDA–lesioned rats and the dyskinetic MPTP-treated primate), its relevance to humans is uncertain, and it is difficult to separate the changes caused by L-dopa treatment from those treatments that induce dyskinesia. The same emphasis has not been applied to intracellular signaling events related to D-2 receptor function to determine the role it might play, and hence the involvement of the indirect output pathway in the external segment of the globus pallidus and, in turn, the subthalamic nucleus. Indeed, once dyskinesia is established, both D-1 and D-2 receptor agonists are capable of inducing the same involuntary movements, although the intensity may be different.[31]

It is obvious that the explanations for the occurrence of wearing off and dyskinesia sound very similar, which reflects the current uncertainty regarding their pathogenic mechanisms. At best, wearing off might be seen as more presynaptic than postsynaptic, whereas dyskinesia is more postsynaptic than presynaptic. With respect to postsynaptic events, different signaling pathways are responsible for the expression of wearing off and dyskinesia, as similar (if not identical) causative factors are invoked. Simplistically, there may be differences in the D-1–mediated indirect output pathway and D-2–mediated direct output pathway, but the reality is that nobody knows.

PHARMACOLOGIC TREATMENT AND DYSKINESIA

In addition to the extent of nigral cell degeneration, the nature of pharmacologic treatment has a significant effect on the emergence of dyskinesia. It appears that using oral dopamine-agonist therapy in patients with early PD is less likely to induce dyskinesia than would occur with L-dopa. A lower prevalence of dyskinesia or rate of emergence has occurred in early oral dopamine-agonist monotherapy studies using ropinirole, pramipexole, pergolide, or cabergoline in comparison with L-dopa treatment.[32–36] However, overall dopamine agonists did not produce the same level of improvement in the Unified Parkinson Disease Rating Scale (UPDRS) scores as seen with L-dopa, and it is not known what would have happened in relation to dyskinesia had clinical efficacy been equal. This initial benefit on prevalence of dyskinesia can be lost in those patients requiring L-dopa supplementation in whom, over time and with disease progression, the differentiation between oral dopamine agonists and L-dopa can become blurred.[6] Three other points are worthy of note. First, results from the agonist monotherapy studies ELLDOPA and STRIDE-PD indicated that dyskinesia can occur early in the course of L-dopa treatment. Second, although L-dopa induced a higher prevalence of dyskinesia, most occurrences were mild and nontroublesome, with no difference in troublesome symptoms in comparison with dopamine agonists, although these were uncommon. This finding reflects the lower degree of nigral cell loss in early-stage PD. Third, in STRIDE-PD, there was a dose relationship to the incidence of dyskinesia, such that at doses less than 400 mg/d the incidence of dyskinesia

(as well as wearing off) was low, which was reflected in the low occurrence of dyskinesia in the comparison of immediate-release (IR) L-dopa (Sinemet) with continuous-release (CR) L-dopa (Sinemet CR), both in combination with carbidopa, reported in the CR Five-Year International Response Fluctuation (CR First) trial.[37]

CONTINUOUS DOPAMINERGIC STIMULATION AND ITS FLAWS

The explanation for the lower incidence of dyskinesia and wearing off associated with the use of dopamine agonists led to the concept of continuous dopaminergic stimulation (CDS), which has been the rationale for treatment with dopamine agonists in the early treatment of PD.[38] In brief, CDS is underpinned by data showing that tonic firing of dopaminergic neurons results in a steady baseline concentration of extracellular dopamine in the striatum, independent of movement. Coupled with high-frequency burst firing in response to movement and the presynaptic buffering of dopamine afforded vesicular storage, this translates into continuous stimulation of postsynaptic dopamine receptors. Consequently, the loss of the buffering capacity in PD as presynaptic terminals degenerate leads to nonphysiologic stimulation of dopamine receptors and subsequently to abnormalities of striatal function. For example, in 6-OHDA–lesioned rats, administration of L-dopa resulted in far more marked increases in extracellular dopamine levels than those seen in healthy rats, as its uptake and storage in dopaminergic terminals had been lost.[39] On repeated L-dopa treatment, extracellular dopamine levels in those 6-OHDA–lesioned rats that developed AIMs were approximately twice those reported in animals not showing involuntary movements.[40] This finding is reflected in humans through the higher striatal synaptic dopamine levels observed in L-dopa–treated patients with PD who exhibited wearing off and dyskinesia when compared with stable responders, as assessed by positron emission tomography (PET).[41] The application of this knowledge to the lower incidence of motor fluctuations and complications produced by dopamine agonists led to the clinical application of CDS.

The plasma half-lives of the 2 treatments are a clear differentiator between oral L-dopa and oral dopamine-agonist administration used in the early agonist monotherapy studies.[34] At a basic level, the short duration of effect of IR L-dopa was related to its rapid clearance from plasma (with a half-life of ~90 minutes), which resulted in a pulsatile nonphysiologic stimulation of striatal dopamine receptors in PD patients. This process was postulated to cause alterations in molecular signaling and genetic changes in basal ganglia, resulting in dyskinesia. By contrast, the more prolonged duration of effect of dopamine agonists linked to their considerably longer presence in plasma was taken as evidence that they could provide a more continuous physiologic dopaminergic stimulation, which resulted in less perturbation of striatal function and less dyskinesia. Indeed, in studies in MPTP-treated primates, a range of dopamine-agonist drugs was shown to induce fewer occurrences of dyskinesia than seen with equivalent doses of L-dopa.[42–44] So far, so good.

However, there is no correlation between the half-lives of the dopamine agonists administered in patients with PD and the prevalence of dyskinesia in monotherapy studies.[34] Cabergoline has the longest plasma half-life but produces the highest incidence of dyskinesia. Commonly used dopamine agonists such as the immediate release formulations of ropinirole and pramipexole are dosed 3 times daily and are not effective over the nighttime period, so they clearly do not result in CDS. The extended-release (ER) compounds of pramipexole and ropinirole taken in the morning produce more stable plasma drug levels over the daytime period[45] but, in general, do not control nocturnal symptoms.

There have been no head-to-head comparisons between orally administered dopamine agonists of differing half-lives or duration of effect that test the validity of CDS. All studies to date have involved comparisons between L-dopa and a dopamine agonist, which may be misleading. In the MPTP-treated primates, where more dopamine agonists have been investigated for the induction of dyskinesia than in humans, no correlation was found between duration of drug effect and dyskinesia induction; however, few head-to-head studies have been conducted.[7,46] In a comparison of dyskinesia induction in MPTP-treated common marmosets treated with the short-acting dopamine agonist apomorphine and the long-acting dopamine agonist pergolide versus L-dopa, which has an intermediate duration of effect, both dopamine agonists produced fewer cases of involuntary movements.[42] Another comparison of subcutaneous administration of the dopamine agonist rotigotine, which is shorter acting than oral L-dopa (see later discussion), in a dose that improved motor function to the same degree as L-dopa, resulted in far lower incidences of dyskinesia.[47] In the 6-OHDA–lesioned rat, however, a better correlation with duration of effect seemed to occur in both induction and expression of AIMs.[48] Plasma half-lives of drugs may not be the best guide to whether CDS is achieved. The partial dopamine agonist pardoprunox has a plasma half-life of 2 to 3 hours, but PET studies have shown that its half-life at striatal dopamine receptors is 11 to 13 hours.

The foregoing discussion suggests that CDS may not explain why differences exist between L-dopa and dopamine agonists for dyskinesia induction. In fact, the differences in dyskinesia induction between L-dopa and dopamine agonists may be more related to pharmacology than to pharmacodynamics or pharmacokinetics. Dopamine agonists such as ropinirole and pramipexole act selectively on D-2/D-3 receptors (D-2–like receptors), and are therefore limited in their pharmacologic effects because 5 dopamine receptor subtypes (D-1–like and D-2–like receptors) exist.[49] By contrast, L-dopa forms dopamine that interacts with both D-1–like and D-2–like dopamine receptors as well as affecting noradrenergic, serotoninergic, and glutamatergic function. Because D-1–like receptors have been implicated in both the reversal of motor deficits and dyskinesia induction in PD patients, it seems feasible that L-dopa has a higher efficacy and greater ability to induce dyskinesia because of its broader pharmacology.[45,46] Indeed, L-dopa and dopamine agonists should not be considered as equivalent drugs but rather representatives of 2 distinct drug classes. There may also be differences in dyskinesia expression related to the pharmacology of dopamine agonists in comparison with L-dopa. Thus, whereas administration of dopamine agonists ropinirole and piribedil to MPTP-treated primates resulted in only a low level of dyskinesia, switching to an equivalent dose of L-dopa immediately invoked intense dyskinetic movements.[50,51] By contrast, switching from L-dopa to an equivalent dose of a dopamine agonist immediately reduced dyskinesia intensity. This finding suggests that dopamine agonists do prime for dyskinesia but do not lead to its expression, whereas L-dopa results in priming and expression, which may ultimately be related to its D-1 receptor activity.

It is interesting that combinations of dopamine agonists and L-dopa have effects dependent on the proportionality of effect. A comparison of pramipexole and L-dopa for dyskinesia induction in MPTP-treated primates showed, as expected, that the dopamine agonist produced far fewer involuntary movements than L-dopa.[52] However, switching the L-dopa–treated animals to a combination of pramipexole with a halved dose of L-dopa maintained the improvement in motor function, but produced no more occurrences of dyskinesia expression when compared with pramipexole alone. These results had been reported in MPTP-treated primates treated with ropinirole plus L-dopa, where an agonist-dominant combination resulted in low levels of

dyskinesia, but an L-dopa–dominant compound caused intense involuntary movements.[53]

MOVING TO CONTINUOUS DRUG DELIVERY

CDS fails to explain differences between L-dopa and dopamine agonists and also fails to explain differences between dopamine agonists of different plasma half-lives, at least in MPTP-treated primates and humans. The validity of CDS requires a belief in the exact nature of changes in striatal dopamine receptors and in basal ganglia output at the cellular and molecular level that leads to the genesis and expression of dyskinesia. To date this is not a certainty, and brings a level of complexity to the application of CDS that is far removed from clinical practice. However, one aspect of CDS may be correct, and may form an easily applicable clinical tenet: namely, the delivery of drugs in PD is important, irrespective of whether it is L-dopa or dopamine agonists, and that CDD is the key to successful treatment. This tenet was the original intention of the concept of CDS, which was based on the use of intravenous and subcutaneous infusions of L-dopa and lisuride in treating PD,[54] but was then appropriated to describe events occurring with oral administration of dopamine agonists. Subsequently, the importance of CDD has been demonstrated in studies using both 6-OHDA–lesioned rats and MPTP-treated primates, and in humans.[7,46,55]

The repeated oral administration of L-dopa to 6-OHDA rats leads to shortening of drug response, sharpening of peak effects, sensitization to dopamine agonists, induction of AIMs, and molecular and receptor changes associated with wearing off and dyskinesia induction.[14,56] The delivery of L-dopa from an intraperitoneal mini-pump avoided sensitization to the effects of apomorphine, suggesting that changes in drug delivery may have beneficial effects. This result appears to be in line with the ability of continuous intravenous and intraduodenal infusion of L-dopa to control wearing off in PD patients, while intraduodenal infusion has also been reported to diminish established dyskinesia over time.[57] Similarly, combining L-dopa with the catechol-*O*-methyltransferase inhibitor entacapone in 6-OHDA–lesioned rats was shown to delay wearing off, decrease AIM induction, and prevent molecular changes in striatum associated with both dyskinesia and wearing off.[58–60] In MPTP-treated primates, a combination of L-dopa and entacapone administered 4 times daily reduced dyskinesia induction alone and in combination with a dopamine agonist, suggesting altered delivery of L-dopa–affected outcome.[61,62] However, this did not translate into a clinically relevant effect when applied in STRIDE-PD in early L-dopa treatment of PD that compared L-dopa/carbidopa with L-dopa/carbidopa/entacapone, or in the earlier CR First study comparing L-dopa/carbidopa IR (Sinemet) with CR (Sinemet CR), where an equivalent prevalence of dyskinesia occurred.[10,37] Indeed, in a recent study of 6-OHDA–lesioned rats, another fly appears in this particular ointment. A comparison of intraperitoneal bolus administration of L-dopa with 8-hour daily intraduodenal infusions found no difference in the rate of induction or intensity of AIMs, although infusion of L-dopa appeared to reduce the duration of established AIM expression over each treatment day.[63] This result again suggests that there is something intrinsic to L-dopa that underlies its ability to induce dyskinesia.

The role of CDD in the effects of dopamine agonists in PD seems clearer. In MPTP-treated monkeys the highly selective D-2 receptor agonist, U-91356A, administered by repeated subcutaneous injection, reversed motor deficits but resulted in progressive dyskinesia.[64] By contrast, continuous infusion with an osmotic mini-pump implanted subcutaneously resulted in only mild transient dyskinesia. Similarly, although repeated daily subcutaneous administration of apomorphine to

MPTP-treated primates induced dyskinesia within 2 weeks, continuous delivery of the drug from a subcutaneously implanted slow-release polymer rod system did not produce dyskinesia, even after 6 months.[65] In addition, low levels of dyskinesia seen following repeated oral treatment with ropinirole were reduced even further by the continuous infusion of the drug.[66] These data emphasize the advantages that CDD can provide and its ease of application in the treatment of patients with PD, and reflects the results obtained using both subcutaneous infusion of apomorphine and intraduodenal infusion of L-dopa in patients with motor fluctuations and motor complications.[67] However, both are invasive technologies and are therefore limited to specific patient populations.

ROTIGOTINE, AN ARCHETYPAL APPROACH TO APPLYING CDD IN THE CLINIC

CDD in patients with PD can be achieved through the use of subcutaneous infusion of apomorphine or the intraduodenal administration of L-dopa, although, as previously stated, this can be invasive and technically challenging.[46] CDD is not achieved by the routine use of ER forms of oral dopamine agonists or CR oral L-dopa. It is achieved, however, with the continuous 24-hour delivery of rotigotine using a transdermal patch, which consequently is used here to illustrate the concept of CDD and its application to clinical use in PD.

Rotigotine is a D-3>D-2>D-1 dopamine agonist that exerts interesting functional interactions with 5-HT_{1A} and α-2B adrenergic receptors (**Table 1**).[68] Rotigotine was originally considered as a development candidate for oral administration in patients with PD. However, while effective in reversing motor deficits in 6-OHDA–lesioned rats and MPTP-treated primates (**Table 2**),[69–73] its duration of action was short[74] although it correlated with plasma drug levels.[75] Of importance, rotigotine was shown to be effective after application to the skin in both 6-OHDA–lesioned rats and MPTP-treated primates, producing effects on motor disability that lasted 48 to 72 hours in comparison with 90 minutes after oral administration (see **Table 2**).[71,76]

Table 1
Rotigotine receptor binding profile

Receptor	K_i (nM)
Dopaminergic	
D1	83
D2	17
D3	0.71
D4	15
D5	6.3
Serotonergic	
5-HT_{1A}	30
5-HT_{1D}	853
5-HT_7	86
Adrenergic	
α-2A	338
α-2B	27
α-2C	135

Data from Scheller D, Ullmer C, Berkels R, et al. The in vitro receptor profile of rotigotine: a new agent for the treatment of Parkinson's disease. Naunyn Schmiedebergs Arch Pharmacol 2009;379(1):73–86.

Table 2
Effects of rotigotine in animal models of PD

Preparation	Result of Rotigotine Treatment
6-OHDA–lesioned rat[69,73,76,81]	
Acute treatment	Dose-dependent contralateral rotation
Repeated treatment	No sensitization or tolerance; few AIMs
Continuous treatment	Contraversive rotations; no observed AIMs
MPTP-treated primate[47,71]	
Acute treatment	Increased locomotor activity Reversed motor disability
Repeated treatment	Increased locomotor activity Reversed motor disability Low-intensity dyskinesia
Striatal microdialysis/slice[72,76–79]	
Acute treatment	Dose-dependent decrease in striatal dopamine release Decrease in striatal dopamine metabolites also observed
Continuous treatment	Dopamine levels decreased to 20% of control over 48 h

Abbreviations: 6-OHDA, 6-hydroxydopamine; AIMs, abnormal involuntary movements; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Subsequently, in vivo microdialysis studies showed that rotigotine modified striatal dopamine levels[73,77,78] and that the continuous delivery of the drug resulted in constant levels in the striatum which, importantly, resulted in a continuous activation of dopamine receptors (see **Table 2**).[79] From this starting point, technology was developed for its transdermal delivery in PD patients resulting in constant plasma levels over 24 hours.[80]

In subsequent studies, the potential advantages of the continuous delivery of rotigotine for the treatment of wearing off and dyskinesia in patients with PD became evident (see next section). In 6-OHDA–lesioned rats, the continuous delivery of rotigotine using an injected slow-release formulation generating sustained plasma levels did not induce the sensitization to drug effect that had been reported with repeated short-acting subcutaneous injection of the drug or with oral L-dopa administration (see **Table 2**).[81] Of note, the continuous delivery of rotigotine did not induce AIMs in rats and altered the pattern of gene change in comparison with both repeated subcutaneous injection of rotigotine and repeated L-dopa treatment.[82] Similar effects have been seen in 6-OHDA–lesioned rats treated with rotigotine-loaded microspheres.[83] In MPTP-treated primates, the repeated subcutaneous injection of short-acting rotigotine induced a lower intensity of dyskinesia than repeated treatment with L-dopa, as expected for a dopamine agonist, and both agents reversed motor disability.[47] However, continuous delivery of rotigotine induced even less dyskinesia than seen on repeated injection, and prolonged the duration of reversal of motor deficits. Once dyskinesia had become established, switching from oral L-dopa treatment or repeated short-acting injections of rotigotine to continuous delivery decreased the intensity of dyskinesia.[84] Conversely, halting continuous delivery of rotigotine and introducing short-acting L-dopa or rotigotine injection enhanced or reintroduced marked involuntary movements. These data illustrate that rotigotine has the advantages of using a dopamine agonist, the ability to minimize the intensity of dyskinesia, and the convenience and effectiveness of applying the CDD approach to treatment that maximizes the duration of response and minimizes the risk of perturbations in striatal function.

Table 3
Clinical studies of rotigotine

Study	No. of Sites/Geographic Location(s)	Study Design	Study Duration	Primary Efficacy Variables	Secondary Efficacy Variables
Early PD					
Parkinson's Study Group,[91] 2003	36 sites USA and Canada	Randomized, multicenter, double-blind, placebo-controlled, parallel-group, dose-ranging	14 wk	Change in UPDRS II and III sum score (BL to EoM)	Change in UPDRS I, II, and III subscores Change in Hoehn and Yahr stage End of treatment responder rates
Watts et al,[95] 2007	50 sites USA and Canada	Randomized, double-blind, placebo-controlled	24 wk	Change in UPDRS II and III sum score UPDRS (II+III) responders	Percent change in UPDRS II and III Change in UPDRS II Change in UPDRS III CGI Hoehn and Yahr stage
Giladi et al,[90] 2007	NA Multinational	Randomized, multicenter, double-blind, placebo- and ropinirole-controlled, parallel-group, dose-ranging	45 wk	Proportion treatment responders	Percent change in UPDRS II and III Change in UPDRS II Change in UPDRS III
Elmer et al,[110] 2012	43 sites USA and Canada	Open-label continuation	6 y	UPDRS II, III, and IV UPDRS II and III responders Motor/dyskinesia assessment CGI Hoehn and Yahr stage Time to adjunctive L-dopa therapy Monotherapy status at end of open-label treatment	

Advanced stage PD					
Babic et al,[108] 2006	5 sites UK, Czech Republic, Croatia	Open-label, randomized, parallel group, multicenter, dose escalation	18 wk	Safety and tolerability	
LeWitt et al,[99] 2007	54 sites USA and Canada	Randomized, double-blind, placebo-controlled, parallel group	24 wk	Reduction in absolute time spent off (BL to EoM) Patient response	Change, % change in absolute and relative on and off time, and on with/without dyskinesia No. of off periods On/off status at waking Change in UPDRS II, III, or IV during on time AUC: absolute time off Clinical pharmacology
Poewe et al,[101] 2007	77 sites EU, South Africa, Australia, New Zealand	Randomized, double-blind, double-dummy, placebo- and pramipexole-controlled, parallel-group	32 wk	Change in absolute time spent off (BL to EoM) Patient response (≥30% reduction absolute off time)	Change, absolute and relative, in on and off time, number of off periods, on/off status at waking Change in UPDRS II, III, or IV during on time AUC: absolute time off PDSS
Other clinical studies					
Trenkwalder et al,[107] 2011	49 sites UK, USA, Africa, Australia, EU, New Zealand	Randomized, double-blind, placebo-controlled, parallel group, multicenter, multinational	22 wk	UPDRS III (early morning) PDSS-2 total	PDSS-2 items NADCS Nocturia

Abbreviations: AUC, area under the curve; BL, baseline; CGI, Clinical Global Impression; EoM, end of maintenance; EU, European Union; NA, not available; NADCS, Nocturnal Akinesia, Dystonia, and Cramps Score; PDSS, Parkinson Disease Sleep Scale; UPDRS, Unified Parkinson Disease Rating Scale.

ROTIGOTINE IN CLINICAL USE IN PD

Rotigotine has been available in Europe for several years, having received favorable acceptance for its convenience, ease of use, and efficacy in controlling motor symptoms of PD.[85–88] In clinical trials, the once-daily application of the rotigotine transdermal patch (Neupro) produced dose-related improvements in UPDRS (parts II and III) combined scores, with rapid upward dose titration and allowance for L-dopa dose reduction, and was safe and well tolerated in both the short and long term (**Table 3**).[89–95] Moreover, the once-daily regimen led to a high degree of compliance.[96] In routine clinical practice, the use of the rotigotine patch has allowed some reduction in other PD medications, improved sleep quality, and reduced nocturia.[97]

In later-stage PD in patients exhibiting motor fluctuations and motor complications, the introduction of continuous delivery of rotigotine resulted in a significant dose-related reduction in "off time" while allowing a reduction in L-dopa dosage without any loss of control of motor symptoms and effects similar to those of pramipexole treatment.[98–102] This finding is consistent with the concept that CDD is effective in controlling the motor fluctuations of wearing off. "On time" without dyskinesia increased in most patients but did not reach statistical significance. Similarly, on time after awakening without dyskinesia more than doubled after the introduction of rotigotine, and an improvement in early-morning akinesia was observed.[103] In short, improvements in sleep and motor function on awakening resulting from CDD were achieved with the rotigotine transdermal system.[104–107] These improvements in off time, sleep, and quality of life demonstrate the advantages of CDD through the nighttime period. Moreover, a more rapid escalation of dose did not produce an increase in adverse events than those seen with a slower incremental rate,[108] and switching from oral dopamine-agonist therapy to rotigotine patch treatment was easy and effective.[109]

In the treatment of early PD, the potential of CDD for avoiding dyskinesia induction has been observed. Use of the rotigotine patch markedly improved motor function and diminished the need for L-dopa, in terms of both the number of patients requiring treatment compared with the placebo-treated group and the dosage used.[98,110] The majority of studies were too short to merit comment on dyskinesia induction, but in long-term (up to 6 years) open-label extension studies, the efficacy of rotigotine was maintained, with an incidence of dyskinesia of 25% and with involuntary movements most commonly occurring after the introduction of L-dopa.[110]

SUMMARY

The long-term treatment of PD requires consideration regarding the nature of dopaminergic treatment used to control motor symptoms, in both the early and late stages of the illness. The concept of CDS has altered the face of treatment by persuading clinicians that early use of a dopamine agonist can protect against the onset of wearing off and dyskinesia. However, CDS does not explain many of the preclinical and clinical observations made in relation to the effects of L-dopa and dopamine agonists, and also requires an understanding of the complexities of events occurring at the cellular and molecular level in the striatum, which are themselves uncertain. Rather, an easier mantra for treating PD is to adopt a philosophy of applying drug treatment as continuously as possible, irrespective of whether the therapy is L-dopa or a dopamine agonist. This rule is simple to apply, and reflects what was understood by the original definition of CDS in relation to infusions of L-dopa, apomorphine, and lisuride. Rotigotine delivered by a transdermal patch exemplifies CDD and its ability to control

wearing off and potentially avoid dyskinesia in patients with PD. It also supports the concept of delivering pharmacologic agents continuously in a clear and concise manner that is relevant not only to clinical trials but also to the everyday treatment of PD and to routine clinical practice.

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